UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,133	03/20/2001	Michael P. Vitek	5405.214	3028

20792 7590 02/14/2003

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1622	

DATE MAILED: 02/14/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,133	VITEK, MICHAEL P.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Claims 1-10 are pending.

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to a transgenic mouse whose germ cells and somatic cells contain an inactive iNOS gene and a transgene encoding human iNOS gene and methods of using the mouse for screening of agents that inducing Alzheimer's disease, MS, Inflammatory Bowel Disease, Rheumatoid arthritis or for screening of compounds that treat these diseases.

The specification provides working example for making a transgenic mouse comprising a humanized NOS2 gene by mating a NOS2 knockout mice with a transgenic mouse expressing NOS2. There is no disclosure regarding the characteristics of the transgenic mouse. There is no guidance in the art about the characteristics of a transgenic mouse in which iNOS is inactive and human iNOS is expressed.

In analyzing whether the written description requirement is met, it is first determined whether the complete structure of the claimed invention has been described. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention encompasses a knockout mouse in which a human gene is expressed. Considering the fact that there is no description of the phenotype of the transgenic mouse claimed and the art of making a transgenic animal, including mouse, is unpredictable, the characteristics of the claimed transgenic mouse cannot be predicted. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research. .... A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

This clearly indicates that the phenotype of a transgenic mouse or any animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Additionally, in the instant case, the getting a desirable phenotype or any phenotype in a transgenic mouse is unpredictable because the regulatory sequences that control the expression of a mouse gene and human gene are very different, therefore, one can not predict whether a transgenic mouse can express human gene or at what level and therefore, one can not predict and describe the characteristics of a transgenic mouse, which has inactive iNOS and has human iNOS gene.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed invention.

5. Claims 1-10 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a transgenic mouse whose germ cells and somatic cells contain an inactive iNOS gene and a transgene encoding human iNOS gene and methods of using the mouse for screening of agents that inducing Alzheimer's disease, MS, Inflammatory Bowel Disease, Rheumatoid arthritis or for screening of compounds that treat these diseases.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention,

therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification page 6-8, examples 1-3 disclose working examples for making a transgenic mouse comprising a humanized NOS2 gene by mating a NOS2 knockout mice with a transgenic mouse expressing NOS2. The specification provides a prophetic example to measure NOS2 mRNA and iNOS protein (example 4). Example 5 teaches prophetic example of how to use the claimed mouse. However, the specification fails to provide any guidance or evidence that a human transgene will be efficiently expressed and will follow human pattern of expression in a mouse. Rao (Journal of Toxicology and Environmental Health Part B, 3:27-58, 2000) reviewed the state of the art of molecular mechanism of iNOS expression in different cell types. For example, Rao teaches that the expression iNOS differs with strain and that effect of cytokines and extent of response differs considerably according to species (see second full paragraph on page 28; also see table 1). The art emphasized that it was important to note that a certain agent may have different effects depend on the cell type and species being studied. Therefore, a compound that affects iNOS express in human cell may not affect it in a mouse cell or even differ between different mouse cells or human cells. Additionally, Rao teaches that the promoter elements of human iNOS are less conservative and would be predicted to be nonfunctional based upon their comparison to consensus sequence (see page 41). Taylor et al (Shock 13:413-424, 2000) also discuss the differences in the human and mouse iNOS gene expression (see the entire article, particularly figure 8). The specification does not teach as to how will an artisan get a human pattern of expression when there are differences in mechanisms of regulation of iNOS expression in human and mouse cells. Furthermore, there is no evidence that a mouse with one allele of human gene will develop the diseases if it is unpredictable whether a mouse with both the alleles will develop the disease. In other words, it is unpredictable that a human iNOS promoter will function in a mouse cell and therefore, it is unpredictable whether iNOS protein will be produced in the transgenic mouse so that it can produce recited disease conditions and therefore it is unpredictable whether the agents could be screened in the claimed

methods. Additionally, an artisan would not be able to predict the phenotype of the claimed mouse and therefore an artisan would not know how to use the claimed mouse. It is noted that the specification does not provide any evidence whether the mouse as claimed has any specific characteristics or would be able to develop disease conditions of Alzheimer's disease, MS, Inflammatory Bowel Disease, and Rheumatoid arthritis and therefore, an artisan would not know how to use the claimed mouse. Court has noted:

> "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."

In the instant case, the specification fails to provide sufficient guidance as to how to use the claimed mouse in the claimed methods. It is noted that an artisan will require undue experimentation to use the claimed mouse in the claimed methods because the art of producing a transgenic mouse with a desired phenotype is unpredictable and also it is unpredictable whether human iNOS promoter will function in a mouse to produce a human pattern of iNOS expression and the specification neither provides any evidence that the mouse could express the human transgene nor does it provide guidance to address the issue of unpredictability discussed above.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites "A transgenic mouse whose..... contain an inactive gene.....". The metes and bounds of the claimed invention is not clear because it unclear as to whether the inactive gene is referred to the endogenous gene of the mouse or to an externally provided gene". Additionally, it is unclear as to whether the transgene is integrated in the genome of the cells of the mouse. The claimed invention is also not clear as to what is meant by "a human pattern of expression".

Claim 3 is vague and indefinite because it is unclear as to what is meant by the term "said mouse for one the development of said disease".

The antecedent basis for the term "a mouse" and "said mouse" in claims 2-10 is not clear. It is not clear as to what mouse in claim 1 claims 2-10 refer to and it is also unclear as to whether claims 2-10 refer to the same mouse of claim 1. Use of the term " The transgenic mouse of claim 1" is suggested in claims 2-10 in place of "a mouse of claim 1" or "a transgenic mouse of claim 1".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woi et al (Nature 375: 408-411, 1995) in view of Chartrain et al (The Journal of Biological Chemistry 269:6765-6772, 1994) and Cameron (Molecular Biotechnology 7:253-265, 1997).

Claims are drawn to a transgenic mouse whose germ cells and somatic cells contain an inactive iNOS gene and a transgene encoding human iNOS gene.

Woi et al teach iNOS knockout mice, which have altered immune responses (see the figure 1 and rest of the article for description of the methodology for making the mouse and the characteristics of the mouse). This art does not teach a transgenic mouse which contains inactive iNOS gene and contains human iNOS.

Chartrain et al teach the cloning, structure and characterization of the human iNOS gene (see the methods section and results sections and figure 1) and compare the mouse and human genes (see discussion) and that there was a need to carry out functional expression studies to define the role of different parts of the promoter.

Cameron reviews the state of the art of making of transgenic mouse and developments in the field. The method teaches general methods of making a transgenic mouse.

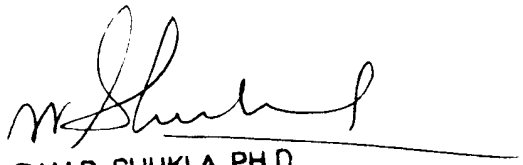
At the time of the invention, it would have been obvious to an artisan of ordinary skill in the art to make a transgenic mouse comprising the human iNOS gene by using the ES cells or eggs of the transgenic mouse of Wei et al with a reasonable expectation of success. An artisan of skill would have been motivated to make such a transgenic mouse because as taught by Chartrain et al, the human gene needed to be characterized and the transgenic mouse of Wei et al would have allowed to define the function of the human iNOS gene in a mouse which lacked its endogenous iNOS gene.

11. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.



RAM R. SHUKLA, PH.D
PATENT EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632